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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/082,780	02/22/2002	S. Christopher Davis	0194.310US	2044

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EXAMINER	
EPPERSON, JON D	

ART UNIT	PAPER NUMBER
1639	

DATE MAILED: 09/09/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/082,780	DAVIS ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 Feburary 2002*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/17/03 11/6/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. Receipt is acknowledged of the claim set filed February 22, 2002.

Status of the Claims

2. Claims 1-29 are pending and examined on the merits. Please note that original claims 1-28 and 30 were renumbered as claims 1-29 by the Examiner in accordance with 37 CFR 1.126, because claim "29" was improperly skipped in the original claim set (i.e., the claims were not numbered consecutively).

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98 (b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on the form PTO-892, they have not been considered.

4. The references listed on applicant's PTO-1449 form have been considered by the Examiner. A copy of the form is attached to this Office Action.

Specification

5. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code such as www.expasy/.ch/enzyme/ (e.g., see page 8, line 4; see also page 9, line 24, etc.), and others throughout the specification. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

6. The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claims Rejections - 35 U.S.C. 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-4, 6, 8-23, 25, and 27-29 are rejected under 35 U.S.C. 102(b) as being anticipated by Reetz et al. (Reetz, M. T.; Becker, M. H.; Klein, H.-H.; Stockigt, D. "A Method for High-Throughput Screening of Enantioselective Catalysts" *Angew. Chem. Int. Ed.* **1999**, *38*, 23, 1758-1761) (11/6/02 IDS, reference 5).

For ***claim 1***, Reetz et al. (see entire document) disclose a high-throughput screening method to assay the enantioselectivity of asymmetric reactions of chiral compounds or of prochiral substrates bearing enantiotopic groups wherein isotopically labeled pseudo-enantiomers or pseudo-prochiral compounds are prepared and screened against an enzymatic lipase catalyst, which anticipates claim 1 (e.g., see Reetz et al., concluding paragraph; see also scheme 2 wherein the "high throughput" methodology is disclosed; see also scheme 1 and equations 1-3 for examples of the compound that were tested). For example, Reetz et al. disclose providing a plurality of substrate molecules wherein the plurality comprises two or more substrate molecule types (e.g., see page 1759, equation 1, compounds 15 and 16; see also equation 3, compound 25) wherein at least one of the substrate molecule types has one or more leaving groups (e.g., see page 1759, equation 1, wherein compounds 19 and 20 represent the "leaving groups"). In addition, at least one of the leaving groups is isotopically labeled (e.g., see page 1759, equation 1, compound 20 wherein "deuterium" is used to label the methyl group). Reetz et al. also disclose a "lipase" enzyme that converts one or more of the substrate molecules to two or more products (e.g., see page 1759, equation 1 wherein compound 16 is converted into compounds 18 and 20 i.e., two compounds). Finally, Reetz et al. disclose quantifying the two or more products using mass spectrometry wherein at least one of the quantified products comprises the isotopically labeled leaving group thereby screening for enzyme stereoselectivity (e.g., see figures 1-2 wherein the "ESI mass spectrum" was used to characterize the reactions; see also paragraph bridging pages 1758-1759).

For ***claim 2***, Reetz et al. disclose 1-phenylethyl acetate that contains an acetate/acetic acid leaving group (see Reetz et al., page 1759, equation 1, compounds 19 and 20).

For ***claim 3***, Reetz et al. disclose the use of a lipase (see Reetz et al., page 1759, column 1, paragraph 4).

For ***claims 4 and 6***, Reetz et al. disclose the hydrolysis of 1-phenylethylacetate to give products 17 and 18 in equation 1 (see Reetz et al., page 1759), which contain more eight carbon atoms.

For ***claims 8-9***, Reetz et al. disclose ^{2}H (see Reetz et al., page 1759, equation 1, compounds 16 and 20).

For ***claims 10-12 and 27-28***, Reetz et al. disclose quantification at about <1%, ~5% and 10% conversion of substrate to products (e.g., see figure 2, circles on graph).

For ***claims 13-15***, Reetz et al. disclose pseudo-enantiomers, pseudo-diastereomers, pseudo-meso compounds (see Reetz et al., page 1758, scheme 1; see also figure 2).

For ***claim 16***, Reetz et al. disclose 1-phenylethylacetate, which is an ester (see Reetz et al., page 1759, equation 1, compounds 15 and 16).

For ***claim 17***, Reetz et al. disclose a pseudo-racemate (see Reetz et al., page 1758, Scheme 1(a) and last paragraph, see also page 1759, equation 1; see also figure 2).

For ***claim 18***, Reetz et al. disclose performing the reactions on a "microtiter" plate (e.g., see page 1759, scheme 2), which reads on a "cell growth plate" because Applicants define "cell growth plate" as a "microtiter" plate (e.g., see specification, page 9, line 21).

For ***claim 19***, Reetz et al. disclose a library of mutant lipases created by directed evolution (see Reetz et al., page 1758, column 2, first paragraph; see also page 1759, column 2, first paragraph).

For ***claim 20***, Reetz et al. also disclose gas chromatography prior to ESI-MS (see Reetz et al., page 1759, table 1).

For ***claim 21***, Reetz et al. disclose a high-throughput screening method to assay the enantioselectivity of asymmetric reactions of pseudo-meso substrates wherein isotopically labeled pseudo-meso compound is converted into two or more products via an enzymatic lipase catalyst (see Reetz et al., page 1760, column 1, especially reaction (3) wherein compound 25 represents the pseudo-meso compound; see also page 1758, scheme 1 (c); see also figure 3).

For ***claim 22***, Reetz et al. disclose the use of a lipase (see Reetz et al., page 1760, column 1).

For ***claims 23 and 25***, Reetz et al. disclose compounds 26 and 27 in equation (3) (see Reetz et al., page 1760), which have more than three carbons.

For ***claim 29***, Reetz et al. gas chromatography prior to ESI-MS (see Reetz et al., page 1759, table 1).

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are

such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

10. Claims 1-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Reetz et al. (Reetz, M. T.; Becker, M. H.; Klein, H.-H.; Stockigt, D. "A Method for High-Throughput Screening of Enantioselective Catalysts" *Angew. Chem. Int. Ed.* **1999**, *38*, 23, 1758-1761) (11/6/02 IDS, reference 5) and Bothner et al. (Bothner, B.; Chavez, R.; Wei, J.; Strupp, C.; Phung, Q.; Schneemann, A.; Siuzdak, G. "Monitoring Enzyme Catalysis with Mass Spectrometry" *J. Biol. Chem.* **2000**, *18*, 13455-13459).

For ***claims 1-4, 6, 8-23, 25 and 27-29***, Reetz et al. teach all the limitations stated in the 35 U.S.C. 102(b) rejection above (incorporated in its entirety herein by reference), which anticipates claims 1-4, 6, 8-23, 25, 27-29 and, consequently, also renders obvious claims 1-4, 6, 8-23, 25, and 27-29.

The prior art teaching of Reetz et al. differs from the claimed invention as follows:

For ***claims 5, 7, 24 and 26***, the prior art teachings of Reetz et al. differ from the claimed invention by not specifically reciting the use of leaving groups with more than four atoms that are used in similar screening assays with lipases. Reetz et al. only disclose two carbon atom "acetate" leaving groups and a general formula that would encompass larger leaving groups, but does not explicitly point to any one larger leaving group (e.g., see scheme 1, compounds 5 and 6; see also page 1759, equation 1, compounds 19 and 20).

However, Bothner et al. teaches the following limitations that are deficient in Reetz et al.:

For ***claims 5, 7, 24 and 26***, Bothner et al. (see entire document) teach a dodecanoic acid leaving group catalyzed by lipase hydrolysis (see Bothner et al., page 126, figure 6.6), which reads on claims 5, 7, 24 and 26 because this leaving group contains 12 carbon atoms.

It would have been obvious to one skilled in the art at the time the invention was made to screen for enantioselective catalysts using an electrospray mass spectrometer in conjunction with mass-labeled compounds as disclosed by Reetz et al. using compounds with larger leaving groups like "dodecanoic acid" as disclosed by Bothner et al. explicitly states that substrates like 1,2-O-di-lauryl-rac-glycero-3-lauric acid ester are excellent substrates for lipases especially with regard to kinetic analysis because it showed a "clean conversion" and represents a more "natural" substrate (e.g., see Bothner et al, page 13459, column 1; see also scheme 4), which would encompass the "kinetic resolution of all types of chiral compounds" via lipase hydrolysis as disclosed by Reetz et al (e.g., see

Reetz et al., page 1759, column 2, last paragraph). In addition, one of ordinary skill in the art would have been motivated to use the compounds disclosed by Bothner et al. including compounds **4**, **7** and **8** (e.g., see schemes 2-4) because Bothner et al. teach, "From macromolecular protein dynamics, kinetic measurements, and the effect of unnatural substrates on reaction dynamics, mass spectrometry offers excellent accuracy, reproducibility and is especially well suited for assaying reactions that cannot be followed spectrophotometrically. In cases where introduction of a chromophore drastically changes the fate of the reaction as a result of structural features of the substrate (as illustrated by the resorufin-containing substrate), ESI-MS has been found to be especially valuable. The small sample size, minimal handling requirements, along with the potential for high throughput represent further significant advantages. Accurate mass measurements by ESI-MS also suggest the further utility of this technique for the kinetic analysis of reactions involving enzyme inhibitors" (e.g., see Bothner et al., page 13459, "Conclusion" section). Furthermore, one of ordinary skill in the art would have reasonably expected to be successful because both Bothner et al. and Reetz et al. teach successful examples of monitoring lipase substrates using ESI-MS.

Contact Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (571) 272-0808. The examiner can normally be reached Monday-Friday from 9:00 to 5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (571) 272-0811. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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August 24, 2004

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